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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Karsten HENCO, et al.

Serial No.: 08/157,195 Group Art Unit: 1807

Filed: December 8, 1993 Examiner: P. Tran

Title: PROCESS FOR THE DETERMINATION OF IN VITRO AMPLIFIED NUCLEIC ACIDS

APPELLANTS' BRIEF

Appellants submit the present brief, in triplicate, subsequent to the Notice of Appeal filed October 29, 1996.

(1) REAL PARTY IN INTEREST

The present application has been assigned to Evotec BioSytems GmbH, pursuant to an assignment recorded at Reel/Frame 7153/0047.

(2) RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences.

(3) STATUS OF CLAIMS

Claims 1-66 were canceled. Claims 67-108 are pending, and appealed. Claims 67-108 stand rejected under 35 USC §112. Attached, hereto, as Appendix I are claims 67-108; claims 67 and 75, of which, appear as amended by "third" and "fourth" after final amendments, submitted, concurrently, herewith (see, sections (4), 8(A)(1), and 8(B), infra). Claims 67 and 75 with said amendments appearing as deletions in brackets and additions underlined are found in Appendix II, attached, hereto.

Claim 75 stands rejected under 35 USC §112, first paragraph. Claims 93-96 stand finally rejected under 35 USC §112, first paragraph. In the "final" action, which

was mailed April 29, 1996 (the "final action"), the rejections were set forth in separate numbered paragraphs; that is, paragraphs 7-14. In subsequent advisory actions mailed October 29, 1996 (the "first advisory action"), and February 3, 1997 (the "third advisory action") the rejections from the final action found in paragraphs 8-11 and 14 were withdrawn ("overcome" by responses filed September 30, 1996 and January 14, 1997).

The only rejections found in the final action that were not, subsequently, withdrawn are the rejections found in paragraphs 7, 12, and 14; which are the rejections currently appealed, as set forth in the first paragraph of this section.

Furthermore, the rejection found in paragraph 12 of the final action is deemed to be overcome by the amendment after final rejection submitted, concurrently, herewith; as further explained in the following sections 4 and 8 of the instant brief.

Claim 109, which was submitted as part of the amendment filed December 30 , 1996, was not entered, in accordance with the advisory action mailed January 8, 1997.

(4) STATUS OF AMENDMENTS

An amendment submitted after final rejection on December 30, 1996, was not entered, in accordance with the advisory action mailed January 8, 1997 (the "second advisory action"). An amendment submitted after final rejection on January 14, 1997, was entered in accordance with the third advisory action.

Third and fourth amendments, after final rejection, are submitted, concurrently, herewith; in order to reduce the issues on appeal (as discussed, in detail, in sections (8)(A)(1) and (8)(B), infra).

(5) SUMMARY OF INVENTION

The instant invention, as most broadly defined in claim 67 is a "process" for analyzing amplified (that is, replicated) DNA, wherein the amplification is, optionally, performed; that is, the amplification and analysis are, optionally, "carried out in a sealed reaction chamber (measuring compartment) without intermittent opening" (specification, page 4, last paragraph). In the claimed process, the analytical procedure is carried out by contacting the DNA with a "probe" that has a spectroscopically measurable parameter and the capacity to interact with the DNA (such as a probe that hybridizes with the DNA or a probe that intercalates with the DNA) (specification, page 7, first paragraph, and page 15, last paragraph); denaturing the DNA, which has interacted with the "probe," whereby a variation is effected in the spectroscopically measurable parameter of the probe, such that a corresponding change in a signal emitted by the probe ("measurable signal") is detected (specification page 4, lines 19-30).

The presently claimed "process" allows, for example, the detection of point mutations, deletions, insertions, and rearrangements within the DNA or RNA (specification, page 13, lines 6-9).

(6) ISSUES

The issues presented on appeal are: (a)(1) whether claims 67-108 were properly rejected under 35 USC §112, second paragraph, based on use of the word "interacts" (that is, whether "interacts" is indefinite); (A)(2) whether the rejection of claims 67-108

under 35 USC §112, second paragraph, is overcome by adding to the claims **--wherein said probe is an oligo- or polynucleotide that hybridizes with the nucleic acid, a dye that intercalates with the nucleic acid, or a combination thereof--** (assuming entry of the after final amendment submitted, concurrently, herewith, which modifies the claims, accordingly); (B) whether the amendment submitted, concurrently, herewith that changes **"homogenous phase"** in claim 75, line 2, to **--free solution--** overcomes the rejection of claim 75 under 35 USC §112, first paragraph (assuming entry of said amendment); and (C) whether claims 93-96 are properly rejected under 35 USC §112, first paragraph.

(7) GROUPING OF CLAIMS

Claims 67-108 do not stand or fall together in view of the rejection of these claims under 35 USC §112, second paragraph, based on use of the word "interacts"; claims 68, 70, 71, 75, 76, 77, 78, 80-85 and 93-96 are independently patentable.

(8) ARGUMENT

A. § 112, Second Paragraph Rejection

(1) The word "interacts" is not indefinite.

Claims 67-108 stand rejected under 35 USC §112, second paragraph, because the examiner considered the word "interacts" to be indefinite. The rejection is improper for the following reasons.

With all due respect, the examiner confuses the function of the claims with the function of the specification. The claims define the legal limits of the invention;

whereas, the specification details how to make and use the invention. In re Roberts, 176 USPQ 313, 315 (CCPA 1973). The test for indefinite claim language under the second paragraph of §112 is whether one of ordinary skill in the art would be confused as to the subject matter circumscribed by the claims. In re Kroekel, 183 USPQ 610 (CCPA 1974). The rejection under §112, second paragraph, for alleged indefinite claim language "can not stand" based on a word recited in the claims, which "may be read in theory to include compositions that are impossible in fact to formulate." In Geerdes, 180 USPQ 789, 793 (CCPA 1974). The "use of materials which might present achievement of the objective (by making the process inoperative) can hardly be said to be within the scope of claims." Id. Furthermore, the Board of Patent Appeals and Interferences has declared that is will not read claims in such a manner that a word in the claims would be construed to include an inoperative embodiment. Tsuchiya v. Woods, 220 USPQ 984 (P.O. Board of Patent Interferences 1983).

In the present situation, one of ordinary skill in the art would have no difficulty, whatsoever, understanding what is intended by the term "interact" as recited in the present claims. Since the claims can not be construed in such a manner that the word "interact" would include any material that would not function as the "probe" recited in the instant claims, Geerdes, Woods, the word "interact" is not indefinite claim language proscribed under the second paragraph of §112 of the statute.

In accordance with the Examiner Interview Summary (recording the interview dated March 6, 1997) the examiner appears to require that claims be limited to

"polynucleotide probes, when the probe interacts by hybridization" and "a dye, when the probe interacts by intercalation." However, as mentioned above, this would confuse the function of the claims with the function of the specification. That is, how the probe "interacts" with the "nucleotide" is irrelevant with respect to the claim; that is , whether by hybridization or intercalation. As long as the probe "interacts" such that denaturation of the nucleic acid "effects variation in the spectroscopically measured parameter of the probe, creating a measurable signal" (claim 67, lines 10-13), the requirements of the claim are fulfilled. The "absence in the claim of specific steps which would bring about the desired [function] is no defect. The claims define the limits of the claimed invention, and it is the function of the specification to detail how this inanition is to be practiced." Roberts, 176 USPQ at 315.

Reason for the rejection found in paragraph 7 of the final office action was that the word "interacts" is broad, that is, generic; it reads on both hybridizing and intercalating. Broad terminology in a claim cannot be rejected as indefinite simply because it is broad, that is, generic. Claim "breadth is not to be equated with indefiniteness." In re Miller, 169 USPQ 597, 600 (CCPA 1970). Although a generic expression in a claim covers more than one embodiment, "the expression is not for that reason indefinite." In re Skoll, 187 USPQ 481, 482-83 (CCPA 1975). Accordingly, the rejection in paragraph 7 of the final action is legally improper.

Furthermore, appellants respectfully submit that, as disclosed in the present specification, "interacts" represents a justifiable generic term. In addition to effecting

hybridization, the embodiment of the presently claimed invention shown in Figure 2 demonstrates a substance, which interacts by ***intercalating*** with the nucleic acid to be analyzed. Intercalation is known in the art to represent a different process than hybridization. Hybridization defines the precise interaction between the nucleotides of a probe, on the one hand, with the complementary nucleotides of a nucleic acid, on the other. Intercalation defines a process, which effects a more-or-less known-specific substrate binding; for example, the binding of an ethidium bromide fluorescent dye to a nucleic acid. In accordance with the foregoing explanation, the generic term "interacts" is appropriate under the present circumstances.

The claims identified in section (7), supra, do not stand or fall together with the remaining claims subject to this rejection. Each of the claims identified in section (7) contains a limitation on the recited "probe" that "interacts with the nucleic acid." The only reason provided by the examiner to support the allegation that the word "interacts" is indefinite that it is allegedly unclear whether the term means "that the probe intercalates with or hybridizes to the amplified nucleic acid" (final action, page 2, penultimate line, through page 3, line 2). On the other hand, each of the claims identified in section (7), supra, limits the word "interacts" to mean (either expressly or impliedly) hybridization or intercalation, or a combination of hybridization and intercalation. Since each of these claims is limited in a manner that resolves (that is, renders moot) the reason set forth to support the rejection, the rejection of these claims under §112, second paragraph, is improper, on its face.

(2) The "third" amendment after final overcomes the rejection.

Submitted, concurrently herewith, is a "third" after final amendment that limits the term "interact" to **--polynucleotide probe that interacts by hybridization, a dye that interacts by intercalation, or a combination thereof--**. This amendment is submitted in order to reduce the issues on appeal; in view of the comments made by the examiner in the "summary" of the interview occurring March 6, 1997. Should the amendment be entered, and the rejection under 35 USC §112, second paragraph, of claims 67-108 be withdrawn, and the other amendment after final submitted, concurrently herewith, be entered, resulting in a withdrawal of the rejection of claim 75 under 35 USC §112, first paragraph, and the rejection of claims 93-96 under 35 USC §112, first paragraph, be withdrawn as being moot (as explained, infra), the present appeal, and appeal brief, would be rendered unnecessary.

B. Rejection of Claim 75 Is Overcome by Amendment

Filed, concurrently, with the present brief is a "fourth" after final amendment that changes "homogenous phase" to --free solution-- in claim 75, line 2. Since all occurrences of the phrase "homogeneous phase" are removed from the claim, the rejection is overcome (assuming that the amendment is entered).

C. Rejection of Claims 93-96 Under §112, First Paragraph, Was Overcome by Previously Entered Amendment

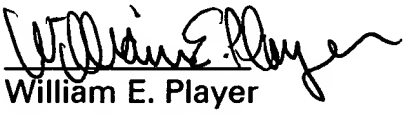
The only reason set forth for the rejection of claims 93-96 under 35 USC §112, first paragraph, (as set forth in paragraph number 14 of the final action), was

appearance of the language "at least one non-naturally occurring chemical structural element" (final action, page 5, lines 13-19). The after final amendment filed January 14, 1997, which was entered in accordance with the third advisory action, deleted the language **"non-naturally occurring"** from claims 93-96. Thereby, the claim language is identical to that found of original claim 27; that is, the claims now read **--at least one chemical structural element--**; which language was not subject to this rejection (and, by being in the original claims, is part of the original disclosure). Since the exact language that is now present in the claims was present in the original disclosure of the application (which includes the original claims), there can be no lack of descriptive support under §112, first paragraph. Since the amendment filed January 14, 1997, rendered moot the sole reason for the rejection under 35 USC 112, first paragraph, of claims 93-96, the rejection was overcome.

CONCLUSION

For the foregoing reasons, reversal and/or withdrawal of all rejections of record is requested.

Respectfully submitted,

By: 
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APPENDIX I

CLAIMS

67. A process for the qualitative and quantitative analysis, in a reaction means comprising a sealed reaction chamber, of at least one in vitro amplified nucleic acid in a sample comprising the steps of:

- including in the sample, during or subsequent to amplification of the nucleic acid, at least one probe which interacts with the nucleic acid to be detected, said probe being an oligo- or polynucleotide that hybridizes with the nucleic acid, a dye that intercalates with the nucleic acid, or a combination thereof, and having a spectroscopically measurable parameter;
- exposing the sample to the action of a gradient that, at least partially, denatures the amplified nucleic acid in the sample and that effects variation in the spectroscopically measurable parameter of the probe, creating a measurable signal;
- detecting the measurable signal; and
- optionally carrying out the amplification reaction and the qualitative and quantitative analysis without opening the sealed reaction chamber.

68. The process according to Claim 67, wherein the spectroscopically measurable parameter of the probe is at least one luminescent or fluorescent dye, and the probe includes a nucleic acid portion, which interacts with the in vitro amplified

nucleic acid during the denaturation accompanied by a change in the measurable signal.

69. The process according to Claim 67, wherein the measurable signal is detected (a) using wave length variation, shift in luminescence or fluorescence intensity, variation in fluorescence polarization, variation in excited state lifetime, or a combination thereof, or (b) using the principle of energy transfer, or (c) through a concentration effect.

70. The process according to Claim 67, wherein the spectroscopically measurable parameter includes a plurality of dyes distinguishable from each other spectroscopically.

71. The process according to Claim 70, wherein a laser excites luminescence of the dyes.

72. The process according to Claim 67, wherein the reaction mixture includes at least one co-amplified nucleic acid standard, the sequence of which is homologous to a sequence to be analyzed, with the exception of at least one point mutation.

73. The process according to Claim 67, that includes at least one co-amplified nucleic acid standard having a primer region, the sequence of which is homologous to the primer region of the amplified nucleic acid.

74. The process according to Claim 73, wherein the nucleic acid standard is a natural component of the amplified nucleic acid.

75. The process according to Claim 67, wherein amplification is carried out (a) in free solution or (b) using a primer attached to a solid phase, the amplified nucleic acid hybridizes with the probe, and the analysis is determined either attached to the solid phase or within the free solution.

76. The process according to Claim 73, wherein the probe is at least one molecule of fluorescent dye linked to a nucleic acid molecule, the sequence of which is identical or homologous to the amplified nucleic acid to be detected or to the co-amplified nucleic acid standard.

77. The process according to Claim 76, wherein the fluorescent dye linked to the nucleic acid molecule is added to the reaction mixture after completing amplification, and is hybridized with the amplified nucleic acid by thermal denaturation with subsequent renaturation.

78. The process according to Claim 76, wherein the fluorescent dye linked to the nucleic acid molecule is added to the reaction mixture prior to completing amplification, and the probe is a non-amplifiable double-stranded RNA or a non-amplifiable chemically modified nucleic acid.

79. The process according to Claim 67, wherein a primer of a primer pair is used for the amplification, which primer encodes a G:C-rich region at the 5' terminus of preferably from 15 to 20 G:C residues.

80. The process according to Claim 67, wherein the probe is an oligo- or polynucleotide having at least two chemical structural elements, wherein (a) each chemical

structural element can be detected, upon interacting with electromagnetic waves, by absorption or emission of radiation and (b) one of the structural elements, upon interacting with electromagnetic waves, can link to another position on the oligo- or polynucleotide.

81. The process according to Claim 80, wherein the chemical structural elements have a chromophoric system.

82. The process according to Claim 81, wherein the chromophoric system luminesces via a dye substituent thereon.

83. The process according to Claim 80, wherein the chemical structural element that can link to another position on the oligo- or polynucleotide is a photochemical crosslinker.

84. The process according to Claim 83, wherein the photochemical crosslinkers are psoralene or a psoralene derivative.

85. The process according to Claim 80, wherein spacing between the two chemical structural elements is between 8 to 12 nucleotide positions.

86. The process according to Claim 67, wherein the reaction means comprises a plurality of recesses in a sheet system, each recess thermally weldable, accommodates ready-for-use reagent mixtures in lyophilized or matrix-bound form, and permits direct optical measurement.

87. The process according to Claim 86, wherein the reagent mixtures are stored in spatially separated matrices, and, subsequent to sealing the reaction chamber, are introduced into the reaction process.

88. The process according to Claim 67, wherein the analysis is effected by microtitration.

89. The process according to Claim 67, wherein the gradient is a time-controlled temperature gradient, and the variation of the spectroscopically measurable parameter is monitored as a function of time, temperature, or time and temperature.

90. The process according to Claim 89, wherein the analysis is by temperature gel electrophoresis, chromatography, or directly in homogenous solution, or a combination thereof.

91. The process according to Claim 90, wherein the presence, number, homology, or combination thereof of the amplified nucleic acid depends on the monitored spectroscopically measurable parameter.

92. The process according to Claim 67, wherein the analysis is effected using a data processing system.

93. The process of claim 67 wherein the probe is an oligo- or polynucleotide having at least one chemical structural element (a) having a stable bond that, upon interacting with electromagnetic waves, is capable of cleavage and subsequent linkage with the amplified nucleic acid and (b) that can be detected, upon interacting with electromagnetic waves, by absorption or emission of radiation, wherein said structural element is not a purine or pyrimidine substituent of naturally occurring nucleotide components.

94. The process of claim 93 wherein the chemical structural element having a stable bond is psoralene or a psoralene derivative.

95. The process of claim 93 wherein the chemical structural element that can be detected luminesces.

96. The process of claim 93 wherein one of the chemical structural elements is located 8 to 12 nucleotides away from another of the chemical structural elements.

97. The process of claim 67 wherein the reaction means includes (A) at least one multiple-well-containing sheet, each well being a reaction chamber that includes the probe for and lyophilized amplification reagents and (B) a sealing sheet cooperating with the multiple-well-containing sheet in a manner independently sealing each reaction chamber with a seal that becomes an interior surface of the reaction chamber.

98. The process of claim 97 wherein the reagents are present in at least one water-soluble matrix.

99. The process of claim 98 wherein the matrix includes a stabilizer.

100. The process of claim 98 wherein the matrix includes a sugar.

101. The process of claim 98 wherein the matrix includes trehalose or saccharose.

102. The process of claim 98 wherein the reagents include amplification primers, buffer components, at least one polymerase, and co-factors.

103. The process of claim 97 wherein the reagents include amplification primers, buffer components, at least one polymerase, and co-factors.

104. The process of claim 97 wherein at least one reaction chamber of the well-containing sheet includes a reagent/probe-containing matrix and the chamber interior surface of the corresponding seal includes hybridization reagents.

105. The process of claim 97 wherein the reaction means is composed of kit systems.

106. The process of claim 67 including computer-controlled, time-dependent thermosetting of the reaction chamber.

107. The process of claim 67 including optical-excitation-effecting emitting of a fluorescence signal and optical detection of the fluorescence signal.

108. The process of claim 107 wherein the excitation is by a laser.

APPENDIX II

CLAIMS 67 AND 75 AS REWRITTEN IN "THIRD" AND "FOURTH" AFTER FINAL AMENDMENTS

67 (thrice amended). A process for the qualitative and quantitative analysis, in a reaction means comprising a sealed reaction chamber, of at least one <u>in vitro</u> amplified nucleic acid in a sample comprising the steps of:

- including in the sample, during or subsequent to amplification of the nucleic acid, at least one probe which interacts with the nucleic acid to be detected, said probe <u>being an oligo- or polynucleotide that hybridizes with the nucleic acid, a dye that intercalates with the nucleic acid, or a combination thereof, and</u> having a spectroscopically measurable parameter;
- exposing the sample to the action of a gradient that, at least partially, denatures the amplified nucleic acid in the sample and that effects variation in the spectroscopically measurable parameter of the probe, creating a measurable signal;
- detecting the measurable signal; and
- optionally carrying out the amplification reaction and the qualitative and quantitative analysis without opening the sealed reaction chamber.

75 (twice amended). The process according to Claim 67, wherein amplification is carried out (a) in [homogenous phase] <u>free solution</u> or (b) using a primer attached to a solid phase, the amplified nucleic acid hybridizes with the probe, and the analysis is determined either attached to the solid phase or within the free solution.